Effects on Proliferation and Differentiation of Multipotent Bone Marrow Stromal Cells Engineered to Express Growth Factors for Combined Cell and Gene Therapy.

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Public Summary:
Human mesenchymal stem cells can be genetically engineered to serve as potent delivery vehicles to provide factors for healing damaged tissues and to combat disease. In the current studies we examined the impact of overexpression of several key growth factors known to promote revascularization and tissue healing. It is important to show that, while the MSCs are delivering factors to other tissues, they are not being affected themselves. We want them to serve as delivery vehicles without reacting to the factors that they deliver. From the growth factors tested in the current studies, we found that the potent angiogenic factor VEGF was safe to deliver from gene-modified MSCs, that the MSCs were not altered by the high levels of VEGF that they were producing, and that this therapy had significant effects on healing damaged tissue in a xenograft model of ischemic injury.

Scientific Abstract:
A key mechanism for mesenchymal stem cells/bone marrow stromal cells (MSCs) to promote tissue repair is by secretion of soluble growth factors. Clinical application could therefore be optimized by a combination of cell and gene therapies, where MSCs are genetically modified to express higher levels of a specific factor. However, it remains unknown how this over-expression may alter the fate of the MSCs. Here we show effects of over-expressing the growth factors bFGF, PDGF-BB, TGF-beta(1) and VEGF in human bone marrow-derived MSCs. Ectopic expression of bFGF or PDGF-B lead to highly proliferating MSCs and lead to a robust increase in osteogenesis. In contrast, adipogenesis was strongly inhibited in MSCs over-expressing PDGF-B and only mildly affected in MSCs over-expressing bFGF. Over-expression of TGF-beta(1) blocked both osteogenic and adipogenic differentiation while inducing the formation of stress fibers and increasing the expression of the smooth muscle marker calponin-1 and the chondrogenic marker collagen type II. In contrast, MSCs over-expressing VEGF did not vary from control MSCs in any parameters, likely due to the lack of VEGF receptor expression on MSCs. MSCs engineered to over-express VEGF strongly induced the migration of endothelial cells and enhanced blood flow restoration in a xenograft model of hind limb ischemia. These data support the rationale for genetically modifying MSCs to enhance their therapeutically relevant trophic signals, when safety and efficacy can be demonstrated, and when it can be shown that there are no unwanted effects on their proliferation and differentiation.